Patentability Under 35 U.S.C. §§ 102 and 103

The Final Office Action mailed January 9, 2001 presented the following rejections:

Claims 1-5 and 7 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Hussain et al. (WO Patent Number 82103768 or equivalent U.S. Patent Number 4,464,378 ('378 patent)). The stated grounds for rejection referenced the prior Office Action (Paper Number 6, mailed April 25, 2000). Briefly, the Office stated that Hussain '378 discloses a "pharmaceutically acceptable nasal dosage form for nasally delivering systemically therapeutic levels of drug e.g., morphine to a warm blooded mammal." More specifically, the Office asserts that the '378 disclosure "teaches a 15mg/O.1mL solution (15%) of morphine at pH 4.5." (See, Paper No. 6, page 4, second full paragraph).

Claims 1-11 and 14-15 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Merkus (5,756,483), for reasons stated in the prior office action. In a related rejection, claims 1-11,14-15 and 32 are rejected under 35 U.S.C. §102(e) as allegedly anticipated by Merkus (5,942,251). Briefly, the Office contends that the Merkus references (U.S. Patents: 5,756,483 and 5,942,251) teach an effective, nasally-administered morphine composition having a specific pH of pH 6.0.

Claims 12-13 were rejected under 35 U.S.C. § 103 (a) as being unpatentable over Merkus (5,756,483) for reasons stated in the prior office action. Claims 30-32 are rejected under 35 U.S.C. §103 (a) as being unpatentable over Merkus (5,756,483) or Hussain et al, for reasons stated in the prior office action. The Merkus and Hussain references are cited as above for allegedly teaching a pharmaceutical composition of morphine for nasal delivery with an acidic pH in the range of Applicants claims.

In response to the Final Office Action, Applicants filed a comprehensive Reply that presented detailed evidence and remarks addressing each of the foregoing rejections (see, Applicants' Reply dated July 9th, 2001). The Reply included an extensive analysis and Declaration by Dr. Steven C. Quay presented under 37 CFR 1.132. Finally, Applicants Reply expressly raised technical and legal inquiries for consideration and clarification by the Office,

with the expectation that the Office's response would place the application in condition for allowance or at least place the record in the application in better condition for Appeal.

A Notice of Appeal was filed with the foregoing Reply, and was received by the Office on July 12, 2001.

To Applicants' disappointment, the Office reports to have entered and considered Applicants' Reply and Declaration—while stating summarily that these submissions do not place the application in condition for allowance (see Advisory Action Paper No. 17, at p. 1). At page 2 of the Advisory Action, the Office sets forth a brief statement as to why the Reply and Declaration was not found persuasive. In particular, the Office states that the submission:

> does NOT place the application in condition for allowance because: of the reasons set forth in the prior office action. It is well settled that newly discovered function does not impart patentable moment to otherwise old and obvious subject matter. In re Swinehart 169 USPQ 226, at 299. The fact is that the claimed subject matter, a morphine composition with acidic pH, is old and obvious and was used for the same purpose as claimed.

This summary dismissal fails to address any of Applicants' detailed evidence and testimony presented in their Reply. Also, the Office declined to consider several technical and procedural points of rebuttal and/or inquiry that Applicants Reply specifically asked for clarification on to place the application in better condition for appeal. The fact that the Office specifically relied on the same "reasons set forth in the prior office action" as the basis for rejecting Applicants' Reply, demonstrates that the Advisor Action declined to address the substance and merits of the Reply—because the detailed facts presented in were not of record for consideration in the prior Office Action.

Accordingly, Applicants respectfully request that the Office reconsider all of the evidence presented in their previous Reply, including the facts and fact-based opinion testimony presented in the Declaration of Dr. Steven C. Quay (which are each incorporated herein by reference). It is hoped that the RCE filed herewith will accord the Office procedural latitude to consider this evidence fully and with particularity, and to provide a detailed response to guide Applicants toward allowance of the case or at a minimum provide a clear record for Appeal.

The following discussion briefly reiterates Applicants' rebuttal evidence and testimony presented in the record responsive to the foregoing rejections.

Applicants respectfully submit that the invention of claims 1-5 and 7 are neither disclosed nor suggested by the Hussain et al. `378 patent (or corresponding WO publication). Notably, currently pending independent claim 1 recites a "pharmaceutical formulation for intranasal administration comprising morphine or pharmaceutically acceptable salt thereof at a pH from about 3.0 to about 7.0".

The Office's rejection of claim 1 relies on the Office's interpretation that the Hussain `378 allegedly teaches "a 15mg/0.1mL solution (15%) ,of morphine at pH 4.5." Applicants respectfully submit that this is not an accurate interpretation of the Hussain `378 reference. In particular, the evidence of record clearly shows that the Hussain `378 disclosure is inoperable—particularly with respect to the alleged teachings of this reference relating to pH and concentration of a morphine formulation. The Office initially dismissed this evidence without substantive consideration, on the following stated grounds:

> Regarding the statement by Dr. Behl and the remarks about the operability of Hussain (US Patent 4,464,378), note that every patent is presumed valid (35 U.S.C. 282), and since (sic) that presumption includes the presumption of operability. See MPEP 716.07.

Applicants challenged this dismissal in the above-noted Reply, on the basis that the so-called "presumption of operability" relied upon by the Office (35 U.S.C. § 282) relates only to subject matter that is claimed in an issued U.S. Patent. Specifically, Section 282 of the Act reads:

> Each claim of a patent (whether in independent, dependent, or multiple dependent form) shall be presumed valid independently of the validity of other claims. . . . (emphasis supplied).

Outside of this limited presumption, statements in a patent specification are not accorded any specific presumption of validity.

Next Applicants' analysis turns to the claims of the Hussain `378 patent, which generically recite methods and formulations comprising, e.g.:

> [A]n analgesically effective amount of morphine, hydromorphone, metopon, oxymorphone, desomorphine, dihydromorphine, levorphanol, cyclazocine, phenazocine, 3-hydroxy-N-methyl-morphinan, lovophenacylmorphan, metazocine, nor-levorphanol, phenomorphan, nalorphine, nalbuphine, buprenorphine, butorphanol, levallorphan, or pentazocine, or a nontoxic pharmaceutically acceptable acid addition salt thereof . . ..

The `378 claims thus recite a laundry list of compounds that are purportedly "analgesically effective" compounds. However, Hussain did not actually make a morphine solution as asserted by the Office, and the claims of the `378 patent clearly do not recite any particular pH or concentration of a nasal solution for any of the broad panel of listed drugs.

On this basis, the alleged teachings of Hussain `378 regarding pH and concentration of a nasal morphine solution are not entitled to the presumption of validity conferred by the Office in reliance upon 35 U.S.C. § 282.

Even if the purported teachings of Hussain `378 relied upon by the Office were in fact entitled to a presumption of validity under 35 U.S.C. § 282 as alleged, which they are not, the Office must still consider all of the evidence presented (see Declaration of Dr. Charanjit Behl filed with the Amendment of October 25th, 2000, each incorporated herein; and Applicants' Reply of July 9th and the accompanying Declaration of Dr. Steven C. Quay) in full, substantive detail. This evidence, and the scientific conclusions based thereon, must be viewed by the Office as presumptively correct--unless the Office provides substantiated evidence that is "inconsistent" with Applicants' evidence and conclusions. See, e.g., In re Marzocchi et al., 169 USPQ 367 (CCPA 1971).

Also irrespective of whether a presumption of validity applies to the Hussain `378 disclosure, Applicants need merely show by "a preponderance of the evidence" that the asserted teachings are inoperable (see, e.g., MPEP § 716.07, cited also by the Office). The evidence now presented in the record is unequivocal in this respect, because it clearly evinces that the alleged teachings of Hussain `378 regarding pH and concentration of an intranasal morphine solution cannot be practiced by the skilled artisan according to the Office's interpretation.

As previously noted in the record, the Office asserts that the protocol of Hussain '378 for making an aqueous nalbuphine hydrochloride solution (citing column 10, example 2) is a direct, operable teaching for preparing a "a 15mgI0.1mL solution (15%) of morphine at pH 4.5." However, Applicants' evidence demonstrates that this interpretation is directly contrary to the understanding of the skilled artisan, is scientifically ill-founded, and would lead to an inoperable result.

Contrary to the Office's position, the protocol of Hussain et al. for making a nalbuphine hydrochloride solution (which the reference proposes would generally translate to a procedure for making a morphine solution) does not teach a final pH adjustment to a value of 4.5. Rather, the pH adjustment to 4.5 is conducted at an intermediate stage, prior to the addition of water to reach final volume, and prior to adjustment of tonicity. Accordingly, this reference is improperly construed as teaching a final pH of any drug solution, particularly morphine sulfate. (See, Declaration of Dr. Steven C. Quay at ¶ 7).

In addition, the Hussain '378 protocol for making a nalbuphine hydrochloride solution is not expressly taught as a useful protocol for preparing a morphine sulfate solution. Rather, the nalbuphine hydrochloride protocol is disclosed, hypothetically without working exemplification, by Hussain as a method that can be "substantially repeated" for making a morphine solution. As set forth in the Declaration of Dr. Quay, at ¶ 8:

> [T]he term "substantially repeated" leaves open all unspecified conditions and parameters of the protocol to routine adjustment, particularly modifications aimed at tailoring the protocol to the specific characteristics of substitute compounds proposed for formulation according to the general protocol (e.g., morphine sulfate, and pentazocine lactate, each proposed as substitutes for nalbuphine hydrochloride). (emphasis supplied).

Thus, the reference presents at best an invitation to select alternate parameters and conditions, which clearly provides, at most, an "obvious to try" teaching that amounts to an "invitation to experiment." As explained in In re O'Farrell, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988) "[i]n some cases, what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful

result, where the prior art gave either no indication or which parameters were critical or no direction as to which of many possible choices is likely to be successful."

In resolving these disparate interpretations of the Hussain '378 reference, the Office must view the facts from the standpoint of the skilled artisan—which clearly favors Applicants' construction of the Hussain `378 disclosure. In this regard, additional testimony provided in the Declaration of Dr. Quay (at ¶ 8) shows that:

> Among the most likely parameters that would be considered for change in this context is adjustment of pH for a morphine sulfate, versus nalbuphine hydrochloride, solution. Simply put, the artisan would not presume from the cited passage that the `378 disclosure teaches a final pH of 4.5 for a morphine sulfate solution, even if one accepts the Office's position that the passage actually teaches this value for a nalbuphine hydrochloride solution. On the contrary, the artisan would more likely interpret the express qualification conveyed by the term "substantially repeated" in the passage, to leave the protocol open to such desired modifications as compound-specific pH adjustment. (emphasis added).

Considering the evidence of record in further detail, the skilled artisan would not have followed the teachings of Hussain `378 in the manner proposed by the Office--to select a pH for a morphine sulfate solution even close to the proposed value of pH 4.5 for a morphine formulation as presently claimed. This conclusion is firmly grounded on the well-known principal that a drug's ability to be delivered systemically across mucosal surfaces generally depends on the degree of ionization of the subject drug. As further described in the accompanying Declaration of Dr. Quay (at ¶ 9):

> It was widely understood at the time of the invention that the degree of ionization of a drug influences the drug's ability to be delivered systemically across mucosal surfaces. The degree of ionization of a particular drug is largely determined by the drug's dissociation constant, the pKa, and the pH of the solution in which the drug is dissolved (The pKa of an acid is equal to the pH at which half of the molecules are ionized and half are neutral). A basic drug would be mostly in its unionized state when dissolved in a solution having a pH greater than the pKa of the drug. Accordingly, basic drug formulations are believed to be best absorbed from alkaline solutions where the pH is greater than the drug's pKa. In the particular case of intranasal formulation chemistry, it was a widely known teaching in the art that basic

> drugs generally show improved absorption across the nasal mucosa into the bloodstream when they are formulated in a basic solution having a pH greater than the dissociation constant of the drug. Therefore, for morphine formulations where the subject drug is a basic drug having a pKa of about 8.0, the artisan would generally have predicted the drug to be best absorbed when formulated in a basic solution, wherein the morphine would be delivered predominantly in its unionized state. (emphasis supplied).

Considering this testimony from the proper standpoint for review it is clear that, for morphine formulations where the subject drug is a basic drug having a pKa of about 8.0, the artisan would typically select a basic delivery solution as close to this value as possible to deliver the morphine predominantly in its unionized state. This direction, which contravenes the Office's position on a art-accepted factual basis, is further explained in Dr. Quay's Declaration (at ¶ 10), as follows:

> Following this reasoning, the artisan would generally consider that solutions of morphine sulfate having a final formulation pH of greater than about 7.0 or 8.0 would allow for better absorption of morphine than lower pH solutions. For example, approximately 90% of the morphine sulfate in a solution having a final pH of about 9.0 would be expected to be in the preferred, unionized state (i.e., morphine free base). On this basis, such a high pH solution would be expected to provide for good absorption of morphine from the solution. In contrast, approximately 99% of the morphine would be predicted to be in an ionized state in a morphine sulfate solution having a pH of 6.0. A person of ordinary skill in the art generally would not have expected that morphine having such a high ionization level would provide for adequate absorption of the drug across the nasal mucosa into the bloodstream. The finding in the present invention that there is a high level of morphine absorption into the bloodstream when administered in formulations at pH 6.0 was therefore unexpected, and is clearly neither disclosed nor suggested by the art of record in the application. Similar results were shown for morphine sulfate at a pH range of about 3.0 to about 5.0 where over 99% of the morphine is also in an ionized state. (Underscores added).

This evidence strongly refutes the interpretation accorded by the Office to the entirely prophetic and unsupported statements of Hussain `378, as they relate to the desired pH of a morphine formulation as claimed by Applicants. The record taken as a whole clearly establishes that general knowledge in the art prior to the invention taught directly away from the instantly

claimed subject matter. As explained in W. L. Gore & Associates, Inc. v. Garlock, Inc., 220 USPQ 303, 312 (Fed. Cir. 1983):

> He [the inventor] proceeded contrary to the accepted wisdom of the prior art by dramatically increasing the rate and length of stretch and retaining crystallinity. That fact is strong evidence of nonobviousness.

Further considering the foregoing evidence, Applicants' results of providing a successful intranasal morphine delivery system characterized by the novel pH values presently claimed must be considered "unexpected" results that are sufficient to overcome any prima facie case of obviousness deemed to be established by the Office. As explained by the Federal Circuit in In re Soni, 34 USPQ2d 1684, 1687 (Fed. Cir. 1995):

> One way for a patent applicant to rebut a prima facie case of unobviousness is to make a showing of 'unexpected results,' i.e., to show that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected.
>
> ***
>
> [T]hat which would have been surprising to a person of ordinary skill in the art would not have been obvious. The principle applies most often to less predictable fields, such as chemistry, where minor changes in a product or process may yield substantially different results.

In addition to these factual considerations, Applicants noted that the alleged "substantially substituted" protocol of Hussain `378 can not be followed to yield a solution of morphine sulfate in the manner currently proposed by the Office. (See, Declaration of Dr. Steven C. Quay, at ¶¶ 11-12). Specifically, the Hussain protocol for nalbuphine hydrochloride teaches to combine 15 grams of nalbuphine hydrochloride with 80 mL of water, then to add enough sodium hydroxide solution to bring the pH of the composition to 4.5, then bring the solution to 100 mL with water. The Office itself specifically concluded that the Hussain `378 patent teaches a morphine sulfate composition "containing 15 mg of morphine sulfate per 0.1 mL of water." The facts presented by Dr. Quay clearly evince that this proposed formulation is inoperable:

> The statement in the `378 patent (Col. 10, Lines 45-49), that this procedure "is substantially repeated, except that 15 grams of morphine sulfate are used in place of the nalbuphine hydrochloride", teaches an inoperable protocol, and therefore

> cannot be interpreted in the strict manner proposed by the Office (Note: that the Office itself directly cites the Hussain `378 patent as teaching a morphine sulfate composition "containing 15 mg of morphine sulfate per 0.1 mL of water.") *The flaw in this interpretation of the `378 patent teachings is clearly revealed by the fact that the solubility of morphine sulfate in water would need to be at least approximately 150 mg/mL to achieve the formulation proposed by the Office* (by "substantial" substitution following the actual, nalbuphine hydrochloride procedure). *This solubility is grossly overestimated, and cannot be achieved under normal conditions at ~ pH. This defect is clearly elucidated by the following experiments conducted under my direction* and reported herein as follows: (italics added, underscores in original).

Dr. Quay's Declaration next provides detailed comparative experiments that in one part ("A") are directed to preparation of a morphine sulfate solution "Following Example 2 of U.S. 4,464,378 (as construed by the Office)." (Quay Declaration at ¶ 11). Specifically, 15 grams of morphine sulfate were mixed with 80 mL of water. The pH of the mixture was adjusted to 4.5 with dilute NaOH and stirred for two hours. The volume of the solution was made up to 100 mL with water. The results of this experiment are stated as follows:

> A clear solution was not obtained, indicating that 15 gm/mL of morphine sulfate is not soluble following the foregoing procedure, including intermediate adjustment of the 80 mL solution to pH 4.5.

The second experiment ("B") provided in Dr. Quay's Declaration (at T 11) is directed to "Evaluation of Actual Solubility of Morphine Sulfate in an Aqueous Solution, Before and After pH Adjustment." To estimate the true drug solubility for morphine sulfate in an aqueous solution, the drug was added to water in small increments of about 0.5 gm each to obtain a saturated solution. After the solution was thus prepared, the volume of the solution was made up to 100 mL, and sufficient NaCl was added to adjust the solution to isotonicity. This procedure follows the Office's extrapolation of Example 2 of the `378 patent (directed to preparation of nalbuphine hydrochloride solution). The results of this experiment are summarized as follows:

> Result: The characteristics of the saturated aqueous formulation at 80 mL were as follows:
>
> Water = 80 mL

> Morphine Sulfate added: 4.342 gm + 0.529 gm
>
> NaCl added: 0.218 gm (calculated based on total amount of Morphine Sulfate added.)
>
> These findings indicate that the estimated solubility of morphine sulfate in water is about 50 mg/mL.

In a final experiment, the pH of the saturated morphine sulfate solution prepared in experiment "B" above was adjusted to 4.5, in order to determine the effects, if any, that the pH adjustment would have on solubilization of the morphine sulfate (saturated as indicated at about 50 mg/mL in the non-pH-adjusted solution). To assess this factor, the pH of the solution was adjusted incrementally by slow, stepwise addition of NaOH. After each addition of NaOH, the mixture was stirred for 30 min. (See, Declaration of Dr. Steven C. Quay, at ¶ 11). The result of this last experiment is stated as follows:

> Result: A clear solution of morphine sulfate from the solution set forth in subsection I), above, was not achieved at any elevated pH up to pH 8.12.

In light of these experimental findings, Dr. Quay aptly provides a factually irrefutable conclusion in his Declaration (at ¶ 12) that:

> *The foregoing experimental findings clearly demonstrate that the prophetic disclosure of the Hussain `378 patent regarding the preparation of a morphine sulfate solution (as strictly construed by the Office) is impracticable.* This demonstration casts serious doubt upon all of the teachings of this reference pertaining to morphine formulations, including the desired pH of such formulations for intranasal use, as these teachings have been interpreted by the Office. *The prophetic suggestion to make a blanket substitution of morphine sulfate for nalbuphine hydrochloride in a slavishly copied protocol, which is contrary to the skilled artisan's interpretation of the disclosure for the reasons noted above, renders an inoperable formulation.* Because it is impossible to obtain a morphine sulfate solution "containing lg-5 mg of morphine sulfate per 0.1 mL of water", *there can be no valid scientific significance assigned to any disclosure of a particular pH value of such an impracticable solution.* (italics added, underscore in original).

The fact that this construction of the prior art advanced by the Office would yield an inoperable combination represents compelling evidence of nonobviousness. In re Gordon, 733 F.2d 900, 221, USPQ 1125, 1127 (Fed. Cir. 1984)

Yet additional evidence of record points to the "unexpected results" provided by Applicants' novel morphine formulation. As noted by Dr. Quay in his Declaration (at ¶ 13): "the skilled artisan would ordinarily have looked for additional information, in the patent and elsewhere in the art, to determine a desired pH for (an intranasal morphine) solution." In this context, Dr. Quay concludes that "the artisan would ordinarily have selected a considerably higher pH, e.g., greater than 7.0 or 8.0. in light of the knowledge summarized above concerning the pKa of morphine and the desirability of delivering drugs across mucosal surfaces in an unionized state."

Dr. Quay also critically points to conflicting teachings in the Hussain `378 patent that teach directly away from the intranasal morphine formulations proposed by the Office (e.g., having a supposed pH of 4.5 and a concentration of 150 mg/mL). In particular, the following quotation from the Hussain `378 disclosure (Example 5, at columns 11-12), is cited in Dr. Quay's Declaration (at ¶ 13):

> The following are illustrative aqueous solutions of selected drugs suitable for use as nasal drops or nasal spray. In each case, the pH of the final composition is adjusted to 7.4 . . .. (emphasis added).

In ¶ 14 of his Declaration, Dr. Quay emphasizes that:

> The first identified composition in this Example ('COMPOSITION A') is an aqueous intranasal formulation of nalbuphine hydrochloride. The teaching that the final pH of this nalbuphine composition is to be adjusted to pH 7.4, rather than pH 4.5, is facially inconsistent with the Office's interpretation of the protocol described in Example 2 of this reference, discussed above, and is consistent with my conclusion that the teachings regarding pH adjustment in Example 2 fail to convey a desired final pH adjustment to 4.5-for either a nalbuphine or morphine intranasal formulation.

In summary, the evidence provided in Dr. Quay's Declaration and elsewhere in the record demonstrates clearly that the prophetic formulation method of Hussain `378, as construed

by the Office, yields an inoperable result. The nature of this inoperable teaching relates to the solubility of morphine sulfate in aqueous formulations. To follow the `378 patent teachings for nalbuphine hydrochloride as advocated by the Office, the solubility of morphine sulfate in water would need to be at least approximately 150 mg/mL. As the data provided in Dr. Quay's Declaration clearly establish, this solubility is grossly overestimated, and cannot be achieved under normal conditions at any pH.

These experimental findings clearly demonstrate that the prophetic disclosure of the Hussain `378 patent regarding the preparation of a morphine sulfate solution (as construed by the Office) is "impracticable." If the skilled artisan were in fact motivated to attempt to achieve the 150 mg/mL morphine solution by "substantially" following the nalbuphine hydrochloride protocol, the attempt would necessarily be considered a failure (it is of course not possible to nasally administer a solution that is approximately three-fold over-saturated!) This fact, that it is facially impossible to obtain a morphine sulfate solution following the disclosure of Hussain `378 for nalbuphine hydrochloride, indicates that there can be no valid scientific significance assigned to any disclosure of the reference regarding a particular pH value of an effective, intranasal morphine sulfate solution.

On this basis, and for the other reasons set forth in the record, the rejection of claims 1-5 and 7 under 35 U.S.C. § 102(b) as allegedly anticipated by Hussain et al. (WO 82/03768 or U.S. 4,464,378) is respectfully submitted to be overcome.

With respect to the rejection of claims 1-1 1 and 14-15 under 35 U.S.C. § 102(b) as allegedly anticipated by Merkus (5,756,483), and the related rejection of claims 1-11,14-15 and 32 under 35 U.S.C. §102(e) as allegedly anticipated by Merkus (5,942,251), Applicants traverse on the same grounds. Briefly, the Office contends that the Merkus references (U.S. Patents: 5,756,483 and 5,942,251) teach an effective, nasally-administered morphine composition having a specific pH of pH 6.0. However, the teachings of these two equivalent disclosures have not been properly construed by the Office, as noted above.

Applicants also previously pointed out a clear procedural error relating to the citation of the Merkus patents as prior art references in this application. Specifically, the teachings of Merkus that are relied upon by the Office are not in fact part of the disclosures of the

cited patents. Instead, the subject teachings are expressly represented in the Merkus disclosures as a failed attempt by others (Verweij et al.) to formulate intranasal morphine. This cited Dutch study is specifically criticized for having yielded undesired results, which the Merkus disclosures particularly distinguish from their own teachings (column 6, lines 37-64 of `483 specification; column 6, line 62 to column 77, line 22 of `251 specification). Consequently, it appears that the Merkus references are relied on improperly as the source of the supposed teachings, when in fact the cited material is not a disclosure of Merkus, but is instead presented as a failed attempt by others that therefore teaches away from the presently claimed subject matter.

Consequently, the cited disclosure is not properly of record. Moreover, taken in combination with the Merkus teachings, the disclosure clearly fails not support the Office's position. Briefly, even if the disclosure in the Dutch study (Verwiej et al.) cited by Merkus relating to pH of nasal morphine formulations was properly made of record, the teachings ascribed to this disclosure do not support the Office's interpretation. In particular, the Office asserts that:

> Merkus teaches a pharmaceutical solution formulation of morphine for nasal delivery employing a morphine pharmaceutical salt at a pH of 6 . . . .. See, e.g., column 6, lines 37-50 in US Patent number 5,942,251. (Office Action Paper No. 6, at p. 4, underscore added).

Contrary to this interpretation by the Office, the citation of the Dutch study by Merkus includes the notation "phosphate buffer (0.01 mol/L; pH 6.0)." As indicated in the Declaration of Dr. Steven C. Quay (at 118), "this notation specifies the pH of the phosphate buffer, not of the final formulation achieved by inclusion of the buffer." It is therefore improper to conclude from this notation that the Dutch study teaches any specific pH of a final morphine formulation for nasal administration as presently claimed. As stated by Dr. Quay, the referenced text "should not serve as a scientifically sound teaching relating to the pH of the final solution, only the buffer." (id.)

In addition to the foregoing facts, the disclosures of the Merkus `483 and `251 patents regarding the Dutch (Verweij et al.) study teach directly away from the presently claimed invention--by suggesting that oral morphine formulations are superior to "proposed" nasal morphine formulations in the Dutch study. In particular, the Merkus disclosure (at column 6,

lines 60-64 of `483 patent) directly criticizes and distinguishes the results of the Dutch study, as follows:

> [T]he bioavailability of morphine after giving the nasal spray as described by Verweij and van Gijn is relatively low. After nasal absorption there is no first pass effect and therefore the nasal bioavailability should be higher than the oral. (underscores added).

Merkus additionally notes with skepticism that the bioavailability of morphine delivered intranasally according to the Dutch disclosure was even lower than the oral bioavailability (column 6, lines 54-62 of `483 patent). Accordingly, the Merkus disclosures actually teach away from any disclosure in the Dutch reference regarding effective intranasal morphine solutions. This additional evidence is summarized in the Declaration of Dr. Steven C. Quay (at 120), as follows:

> Based on the Merkus disclosure, the proposed nasally-administered morphine composition (including an unspecified amount of a phosphate buffer with a pH of 6.0) yields a morphine bioavailability that is substantially lower than the bioavailability of orally-administered morphine, which would lead the artisan to administer morphine compositions orally, not nasally. (underscore added).

Now considering the rejection of claims 12-13 under 35 U.S.C. § 103 (a) over Merkus or Hussain et al, these references are also deficient under this Section of the Act for the reasons noted above. The Merkus and Hussain references are relied upon by the Office for the same alleged teachings, i.e., for disclosing a pharmaceutical composition of morphine for nasal delivery with an acidic pH in the range of Applicants claims.

Applicants remarks above, as supported by the accompanying Declaration of Dr. Steven C. Quay, obviate these stated grounds of rejection relating to the teachings of the Hussain and Merkus references. The same deficiencies of these references identified above in the context of the rejections under 35 U.S.C. § 102 are respectfully submitted to obviate the instant rejection of dependent claims 12-13, and 30-32 under 35 U.S.C. § 103.

CONCLUSION

In view of the foregoing, Applicants believe that all claims now pending in this Application are in condition for allowance and an action to that end is urged. If the Examiner believes a telephone conference would aid in the prosecution of this case in any way, please call the undersigned at 206-467-9600.

Respectfully submitted

Dated 2/12/, 02

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